REMARKS

Applicant thanks Examiners Hissong and Landsman for the courtesy of the interview conducted on November 17, 2005.

The specification has been amended to correct a typographical error in the description. Support for the amendment is found particularly in the working examples, wherein increased expression of Fit-1/ST2 is described. No new matter has been added.

The Examiner indicated that only claims 1, 2, 6-8 and 10 were pending in the application. However, Applicant previously canceled only claims 3-5, 9, 11-12, 14, 23-25, 30-33, and 35-36 in the Preliminary Amendment filed November 8, 2001. Therefore, claims 1, 2, 6-8, 10, 13, 15-22, 26-29 and 34 were pending prior to this amendment.

Applicant has amended claims 1, 6-8 and 10 and has canceled claims 2, 13, 15-22, 26-29 and 34. The amendments and cancellations are made without prejudice to pursuing the subject matter deleted by the amendments and/or the canceled subject matter in continuing application(s).

Support for the amendments is found throughout the specification, more particularly as follows. Claims 1 and 6-8 are amended for clarity only. The recitation of antigen binding fragment of antibodies in amended claim 10 is supported in the application, for example at page 22, line 23 through page 24, line 4. The addition of peptide fragments of polypeptides in claim 8 is supported in claim 1 and in several locations in the specification. No new matter has been added.

New claims 37-48 have been added. The addition of claim 37 is supported by original claim 9. The addition of claim 38 is supported at page 2, lines 25-26 (blood), and page 68, lines 21-22 (serum). The addition of claim 39 is supported in original claim 10 and in the specification at page 22, line 23 through page 24, line 4. The addition of claim 40 is supported in original claim 11. The additions of claim 41 and 48 are supported in the specification at, for

example, page 1, lines 32-33; the figures and figure descriptions (e.g., page 8); page 9, lines 2-3; and page 66, lines 25-28. The addition of claim 42 is supported in original claim 9. The addition of claim 43 is supported in the specification at page 2, lines 25-26 (blood), and page 68, lines 21-22 (serum). The addition of claim 44 is supported in original claim 11. The addition of claim 45 is supported in original claim 12. The additions of claim 46 and 47 are supported in the first and second paragraphs of the Detailed Description, and on page 37, lines 20-22. No new matter has been added.

The Fit-1 gene and gene product also is known as ST2 and IL1RL-1 (among other synonyms). The gene is referred to as Fit-1/ST2 throughout this response.

Claims Objections

The Examiner objected to claim 1 as having improper syntax based on the election of Fit-1/ST2. Applicant has amended claim 1 in a manner similar to that suggested by the Examiner. Accordingly, Applicant respectfully requests reconsideration of the claim objection.

The Examiner also objected to claim 2 as being of improper dependent form, again based on the election of Fit-1/ST2. Applicant has canceled claim 2 and respectfully requests reconsideration of the claim objection.

Rejections Under 35 U.S.C. 112, First Paragraph - Enablement

1. The Examiner rejected claims 1, 2, 6-8 and 10 under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement. Claim 2 has been canceled, rendering the rejection of that claim moot.

The Examiner asserts that the specification is not enabling for diagnosing cardiovascular conditions by determining aberrant expression of a fragment of an expression product of Fit-1/ST2. Applicant respectfully disagrees.

With respect to the elected invention, the specification teaches that cardiovascular conditions can be analyzed, for example, by contacting a biological sample with an antibody that binds to Fit-1/ST2 polypeptide. One of skill in the art knows that such assays will identify any Fit-1/ST2 polypeptide that binds to the antibody, i.e., that contains the epitope recognized by the antibody (or epitopes recognized by antibodies in the case of a polyclonal antibody). Thus, naturally occurring polypeptides that are fragments of Fit-1/ST2 polypeptide (e.g., peptides or proteolytic breakdown products of Fit-1/ST2) also will be detected using the assay methods described in the specification.

As a result, one of ordinary skill in the art would not have to use undue experimentation to practice the claimed invention. This is so because the assay methods used to practice the claimed invention are well known in the art, because the person of skill in the art is highly skilled and has significant amounts of knowledge about the assay methods employed, as described above, and further because Applicant has provided a working example of an assay of Fit-1/ST2 polypeptide in a biological sample (Example 2, see page 68). Moreover, Fit-1/ST2 polypeptide sequences and antibodies (as an example of an agent that specifically binds to Fit-1/ST2) were known in the art as of the time that the instant application was filed. Thus, employing a well known assay method to practice the claimed invention will not require exercise of undue experimentation.

Based on these arguments, Applicant respectfully requests reconsideration and withdrawal of the rejection.

2. The Examiner rejected claims 8 and 10 under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement.

The Examiner asserts that the specification is not enabling for diagnosing a cardiovascular condition by monitoring for (1) an antibody that selectively binds a Fit-1/ST2 polypeptide, or (2) a polypeptide that binds the antibody of section (iv) of claim 8. Applicant respectfully traverses the rejection.

Applicant respectfully disagrees that one of ordinary skill in the art is not enabled to practice the invention with respect to assaying for an antibody that binds Fit-1/ST2 polypeptides or peptides. The Examiner asserts that this aspect is not enabled because the "specification does not provide any examples of naturally occurring anti-Fit-1 antibodies, or antibodies against Fit-1 peptides, that are present in a patient with a cardiovascular disorder, and thus indicative of disease." Office Action at page 3. A lack of examples by itself is not a sufficient basis to support the Examiner's conclusion of non-enablement.

The various factors that can be analyzed in determining enablement include (in addition to the presence of working examples as relied upon by the Examiner) the amount of guidance present in the application, the knowledge and level of skill of the person of skill in the art, the quantity of experimentation required, the nature of the invention, and the state of the prior art. In re Wands 858 F.2d 731, 737 (Fed. Cir. 1988).

In the instant case, Applicant has provided sufficient guidance for one of ordinary skill in the art to practice this aspect of the claimed invention without exercising undue experimentation. The type of experimentation require is essentially conducting immunoassays in order to analyze the presence, absence or level of anti-Fit-1/ST2 antibodies. As explained elsewhere herein, Fit-1/ST2 polypeptides were known in the art prior to the filing of the instant application. Thus, one of ordinary skill in the art would have known of such polypeptides and would have been able to utilize the Fit-1/ST2 polypeptides to conduct art-standard immunoassays to determine the presence, absence or level of anti-Fit-1/ST2 antibodies. This type of experimentation was entirely routine in the art and therefore not undue experimentation. Moreover, the level of knowledge and skill in the art was high, which indicates that the person of skill requires commensurately less guidance from the application. In view of at least these Wands factors, Applicant asserts that this aspect of the invention is enabled.

Applicant respectfully disagrees with the Examiner's statements regarding an alleged lack of teaching in the application of Fit-1/ST2 polypeptides "other than those of SEQ ID NO:1 and 3 [*sic*, SEQ ID NO:2 and 4 are Fit-1 polypeptides], which would be capable of binding to an anti-Fit-1 polypeptide." (Office Action at page 3, paragraph 2). Applicant has presented more detailed arguments on this point below. In brief, the notion that one of ordinary skill in the art would not be enabled to practice the invention because there was an alleged lack of teaching of Fit-1/ST2 polypeptides that bind to anti-Fit-1/ST2 antibodies is incorrect; the art was well aware of several Fit-1/ST2 polypeptides (including human Fit-1/ST2) in addition to those described explicitly by amino acid sequence in the specification.

3. The Examiner rejected claims 1, 2, 6-8 and 10 under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement. Claim 2 has been canceled, rendering the rejection of that claim moot.

Applicant appreciates the Examiner's statement that the claimed invention is enabled for diagnosis of cardiovascular conditions based on increased Fit-1/ST2 expression. However, Applicant disagrees with the Examiner's conclusion of a lack of enablement for diagnosis based on aberrant expression of Fit-1/ST2.

Applicant asserts that "aberrant" is a more accurate description of the invention than "increased". Based on the *in vivo* studies of Fit-1/ST2 polypeptide expression in mouse heart and human serum as provided on page 68 of the specification, Fit-1/ST2 expression increases after a cardiovascular event such as acute myocardial infarction and then decreases back to baseline expression. This means that, in assaying multiple samples of a patient having or suspected of having a cardiovascular condition, a practitioner will observe first a relative increase and then a relative decrease in Fit-1/ST2 expression. Each of the observed levels of Fit-1/ST2 expression is "aberrant" as compared to the baseline expression, but as a relative measure the second observed level is decreased, not increased, relative to the first observed level. Accordingly, Applicant believes that "aberrant" is the proper term for the claimed invention.

More generally, the specification teaches one of ordinary skill in the art that expression levels of Fit-1/ST2 different from the normal level (i.e., aberrant expression) are associated with cardiovascular conditions. See, for example, p. 29, lines 1-10, in which aberrant expression is described. Thus the skilled person does not lack for guidance as to the methods needed to examine expression of Fit-1/ST2, and given Applicant's teaching of an association of Fit-1/ST2 expression with cardiovascular conditions, one skilled in the art would reasonably conclude that any deviation from a subject's baseline expression is indicative of a cardiovascular condition.

Regarding the Examiner's objection to a lack of working examples for identification of stages of a cardiovascular condition based on Fit-1/ST2 expression, Applicant notes that the example of human Fit-1/ST2 expression on page 68 of the specification shows that immediately following acute myocardial infarction the level of Fit-1/ST2 expression is elevated, and that as recovery progresses (i.e., another stage of the cardiovascular condition), Fit-1/ST2 expression decreases back to baseline levels.

Applicant also notes that the literature recognizes that mechanical stresses of cardiac tissues can be elevated following a variety of cardiovascular conditions [see Lammerding et al., Ann. NY Acad. Sci. 1015:53-70 (2004), particularly pp53-54; Sussman et al., Circ. Res. 91:888-898 (2002), particularly p. 888; and St. John Sutton et al., Circulation 101:2981-2988 (2000), particularly p. 2981 and Fig. 1]. Copies of these references are included herewith. Thus aberrant expression of Fit-1/ST2 is a diagnostic indicator of such conditions.

Accordingly, based on the amendment of the claims, Applicant respectfully requests that the rejection be withdrawn.

4. The Examiner rejected claims 1, 2, 6-8 and 10 under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement. Claim 2 has been canceled, rendering the rejection of that claim moot.

Applicant appreciates the Examiner's statement that the claimed invention is enabled for the nucleic acids and polypeptides of SEQ ID NO:1-4 (soluble Fit-1 (Fit-1S) and membrane-bound Fit-1 (Fit-1M)). Applicant respectfully disagrees that the claimed invention is not enabled for other Fit-1/ST2 sequences, however.

At the time that the invention was made, Fit-1/ST2 nucleic acid and polypeptide sequences were well known to persons of ordinary skill in the art. Applicant provided two addition sequences of Fit-1/ST2 mouse homologs on page 11, line 6 of the specification: Y07519.1 (SEQ ID NO:13, the truncated soluble receptor from of ST2) and D13695.1 (SEQ ID NO:14, ST2L, the transmembrane form of ST2). Many additional sequences were known, as is evidenced by the following listing (not necessarily exhaustive) of GenBank deposits of Fit-1/ST2 sequences made prior to Applicant's earliest filing date:

GenBank Accession No. (species)	Date of Deposit
AB012701 (human)	31-MAR-1998
AL117622 (human)	15-SEP-1999
AB029084 (human)	18-JUN-1999
D12763 (human)	30-JUL-1992
D12764 (human)	30-JUL-1992
AB022176 (human)	08-JAN-1999
U04319 (rat)	13-DEC-1993
X60184 (mouse)	23-JUN-1991
X60184 (mouse)	23-JUN-1991
E07714 (mouse, associated patent number: JP 1994178687-A)	28-JUN-1994

Due to the knowledge of these numerous deposited Fit-1/ST2 sequences, one of ordinary skill in the art does not need a separate listing of the sequences in the instant application in order for the claimed invention to be enabled. See the discussion below of Capon v. Eshhar v. Dudas (Fed. Cir., August 12, 2005, slip op. pp. 14, 15, 20).

Moreover, one of ordinary skill in the art at the time the invention was filed was highly skilled in the practice of the methods of molecular biology used in the practice of the claimed invention. For example, the binding of agents to nucleic acid molecules (e.g., nucleic acid hybridization) and polypeptides (e.g., antibody binding), with subsequent measurement of the amount bound, was routinely practiced in the art.

Based on these arguments, Applicant respectfully requests reconsideration and withdrawal of the rejection.

5. The Examiner rejected claim 10 under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement.

As basis for this rejection, the Examiner stated that the specification did not "teach the identities of any nucleic acids other than those of SEQ ID NO:1 and 3, and the applicant has not taught how to make a probe/primer that selectively hybridizes to nucleic acids other than those of SEQ ID NO:1 and 3." Office Action at page 5, paragraph 5. The Examiner concludes that, because of this alleged lack of teaching in the specification, one of ordinary skill in the art would not know how to make and/or use any nucleic acids capable of selectively hybridizing to nucleic acids other than SEQ ID NO:1 and 3.

As stated above, the knowledge in the art at the time of filing of the application was such that the person of ordinary skill in the art knew of several Fit-1/ST2 nucleic acids other than SEQ ID NO:1 and 3. Moreover, the skilled artisan knew of, and routinely used, computer programs for identifying and/or designing probes and primers that hybridize to nucleic acids. When these areas of knowledge are combined, it is clear that the person of ordinary skill would have (1) known of multiple Fit-1/ST2 nucleic acids in addition to those of SEQ ID NO:1 and 3, and (2) would have been able to identify readily a probe or a set of primers that hybridize to such Fit-1/ST2 nucleic acids, for monitoring Fit-1/ST2 expression, using only routine experimentation.

Based on these arguments, Applicant respectfully requests reconsideration and withdrawal of the rejection.

6. The Examiner rejected claims 1, 2, 6-8 and 10 under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement. Claim 2 has been canceled, rendering the rejection of that claim moot.

Applicant appreciates the Examiner's statement that the claimed invention is enabled for the Fit-1/ST2 mRNA in cardiac tissue and Th2 lymphocytes. However, Applicant respectfully disagrees that the claimed invention is not enabled for detection of Fit-1/ST2 mRNA or protein in any other tissue or cell type.

The Examiner's attention is directed to page 68 of the specification, in Example 2, wherein Applicant described experiments in which human Fit-1/ST2 protein was detected by an antibody-based assay in blood. One of ordinary skill in the art would understand several things about Fit-1/ST2 detection from the description of this experiment, combined with the knowledge in the art. First, Fit-1/ST2 protein can be detected in the blood. Second, Fit-1/ST2 as a soluble protein can be detected. Third, more Fit-1/ST2 polypeptides than those set forth in SEQ ID NO:2 and 4, i.e., the human Fit-1/ST2 protein, can be detected. Fourth, antibodies capable of use in detecting Fit-1/ST2 were known in the art.

As a result, one of ordinary skill in the art is enabled to detect Fit-1/ST2 in tissues other than cardiac tissue and Th2 lymphocytes, and is enabled to detect Fit-1/ST2 protein.

The Examiner asserts that one of ordinary skill in the art would not know how to use the invention because the art teaches that Fit-1/ST2 is induced in monocytes in response to LPS. Further, the Examiner states that the specification does not teach methods that can be used to discriminate Fit-1/ST2 expression associated with cardiovascular disease from Fit-1/ST2 induced by LPS. From this, the Examiner concludes that it would require undue experimentation to

discriminate Fit-1/ST2 expression "in lymphoid/myeloid cells as it relates to cardiovascular disease from that associated with other conditions." Office Action at page 6.

Applicant disagrees with these conclusions. The Saccani et al. paper describes the induction of Fit-1/ST2 *in vitro* and *in vivo* in response to LPS. The induction of Fit-1/ST2 *in vitro* is exceedingly weak, as is demonstrated by the strength of the signal observed in Figure 1 (compare induction of ST2 in Fig. 1B and the genes induced in Fig. 1A and 1C). It should be noted that the exposure time of the ST2 samples was 2 weeks as compared to 1-2 days for all other samples (see last paragraph of Methods and Materials, p. 779). Comparing the signal strength of the induced genes in Fig. 1 and Fig. 4, and including the 7-14 X longer exposure times, one of ordinary skill in the art can only conclude that ST2 induction by LPS is very weak, and only appears when large amounts of LPS are used.

More importantly, this conclusion is confirmed by the *in vivo* Fit-1/ST2 induction experiment reported by Saccani et al. On page 775, right column, second paragraph, the authors reported that "after stimulation with LPS a very faint transcript, which required 30 days of exposure to be barely visible, was induced in spleen and muscle." Induction of that level would be irrelevant to detection in a diagnostic context.

It should also be noted that Saccani et al. did not demonstrate that Gram negative infection results in LPS-induced Fit-1/ST2 expression, since only LPS was used to induce the weak Fit-1/ST2 expression described above. Thus, one of ordinary skill in the art would not take Saccani's results as indicative of Fit-1/ST2 induction in animals infected with Gram negative bacteria.

Moreover, even if the Examiner's point of view is accepted with respect to LPS stimulation of Fit-1/ST2, the fact that the results of Saccani et al. were known would enable one of ordinary skill in the art to avoid contamination from LPS-induced Fit-1/ST2 expression by excluding from diagnosis persons having a Gram negative bacterial infection.

Finally, Applicant respectfully notes that the requirements for patentability of an invention do not include 100% accuracy or efficacy. The USPTO is not the FDA, that is, not the arbiter of marketability of a product such as a diagnostic kit. A determination of the diagnostic accuracy (e.g., rate of false negative or false positive results) should be left to the agency responsible for such determinations.

Based on these arguments, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rejections Under 35 U.S.C. 112, First Paragraph – Written Description

1. The Examiner rejected claims 1, 2, 8 and 10 under 35 U.S.C. 112, first paragraph, as allegedly lacking an adequate written description. Claim 2 has been canceled, rendering the rejection of that claim moot.

The Examiner asserts that to provide "adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient identifying characteristics of the genus, such as the sequence similarity to the disclosed rat Fit-1 nucleic acids and polypeptides." Office Action at page 6. The Examiner acknowledges that the specification provides rat and mouse Fit-1/ST2 nucleic acid and polypeptide sequences, but concludes that only these sequences are adequately described.

Applicant respectfully disagrees with the Examiner's conclusion. The written description requirement for sequences known in the art as recited in a claimed invention was recently addressed by the Federal Circuit in the case of Capon v. Eshhar v. Dudas (Fed. Cir., August 12, 2005). In that case, the court concluded that with respect to the sequences present in the claimed invention

> "... the law must take cognizance of the scientific facts. The Board erred in refusing to consider the state of the scientific knowledge, as explained by both parties, and in declining to consider the separate scope of each of the claims. None of the cases to which the Board attributes the requirement of total DNA re-

analysis, i.e., Regents v. Lilly, Fiers v. Revel, Amgen, or Enzo Biochem, require a re-description of what was already known." Slip op. at 14.

The court continued:

"The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a per se rule that the information must be determined afresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result." Slip op. at 15.

The court concluded that:

"In summary, the Board erred in ruling that §112 imposes a *per se* rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence is already known in the field." Slip op. at 20.

Thus, in view of the law as enunciated by the CAFC in Capon v. Eshhar v. Dudas, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1, 2, 8 and 10 as lacking an adequate written description.

2. The Examiner rejected claim 10 under 35 U.S.C. 112, first paragraph, as allegedly lacking an adequate written description.

With respect to the peptides recited in claim 10, the Examiner stated that Applicant is "claiming a genus of peptide whose only common feature is homology to the mature Fit-1 polypeptide." Office Action at page 7. The Examiner concludes that the specification does not provide structural or sequence characteristics of such peptides sufficient to provide an adequate written description.

Applicant respectfully disagrees, for the reasons stated above in response to the rejection of claims 1, 2, 8 and 10: the knowledge in the art provides the structural features and sequence features of Fit-1/ST2 polypeptides (and therefore peptides), and this has been deemed sufficient to provide an adequate written description by the CAFC.

Based on these arguments claim 10, Applicant respectfully requests reconsideration and withdrawal of the rejection.

3. The Examiner rejected claim 10 under 35 U.S.C. 112, first paragraph, as allegedly lacking an adequate written description. In particular, the Examiner asserts that the specification does not provide structural features of nucleic acid molecules that hybridize to Fit-1/ST2 nucleic acids, other than SEQ ID NOs:1 and 3.

Applicant respectfully disagrees, for the reasons stated above in response to the rejection of claims 1, 2, 8 and 10: the knowledge in the art provides the sequence of several Fit-1/ST2 nucleic acids, and the knowledge in the art of nucleic acid hybridization is such that the person of skill in the art can readily envision nucleic acids that hybridize to Fit-1/ST2 nucleic acids without a further explicit listing of such hybridizing nucleic acids.

This type of disclosure has been deemed sufficient to provide an adequate written description by the CAFC in the case of Capon v. Eshhar v. Dudas. In that case, known polypeptides were combined to create a new chimeric protein, which the court found to be adequately described. In the instant case, Applicant is claiming the use of known nucleic acid molecules and additional nucleic acid molecules that selectively hybridized to them.

According to Vas-Cath v. Mahurkar, 19 USPQ2d 1111, 1116, as quoted by the Examiner on page 7 of the Office Action, the specification must "clearly allow person of ordinary skill in the art to recognize that [he or she] invented what is claimed." Based on the knowledge of the skilled person as described above, the skilled person would readily recognize that Applicant invented the claimed invention.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claim 10 as lacking an adequate written description.

Rejections Under 35 U.S.C. 112, Second Paragraph

1. The Examiner rejected claims 1, 2, 6-8 and 10 under 35 U.S.C. 112, second paragraph, as incomplete for omitting method steps (see page 8 of Office Action). Claim 2 has been canceled, rendering the rejection of that claim moot.

Applicant respectfully disagrees with the Examiner's assertion that an essential method step is missing. The amended claims recite a method in which increased expression of Fit-1/ST2 nucleic acids and/or expression products is indicative of cardiovascular conditions. Practicing the claimed invention does not necessarily require measuring a control. For example, it may be determined that healthy individuals do not express Fit-1/ST2, or that the blood of healthy patient does not contain Fit-1/ST2 polypeptide. In such cases, any Fit-1/ST2 expression is "increased" and therefore diagnostic. Alternatively, it may be determined that the level of Fit-1/ST2 expressed above a certain baseline amount is to be considered "increased". This type of measure is routinely used in clinical diagnostics. An example of this is provided on page 68 of the application, in which the serum level of Fit-1/ST2 protein was determined. The data presented clearly show that Fit-1/ST2 levels return to a baseline level (~0.8ng/ml) by 14 days post-infarction. In contrast, the level measured in samples of patients one day post-infarction was significantly increased.

Thus, in view of the routine practices in the clinical diagnostic arts, one of ordinary skill in the art would not find that the claimed methods were indefinite.

2. The Examiner rejected claims 8 and 10 under 35 U.S.C. 112, second paragraph, as indefinite.

Applicant has amended claim 8 to recite that the nucleic acid is that recited in part (i) as suggested by the Examiner.

Applicant respectfully disagrees with the Examiner with respect to the rejection of claim 10 as indefinite. The Examiner states that "it is not known what these [hybridization] conditions are." Office Action at page 9. The specification is meant to speak to those of skill in the art. The particular hybridization conditions are not of particular importance in practicing the invention. In other words, one of ordinary skill in the art is familiar with hybridization conditions suitable for practicing the invention. Applicant provided some examples of such conditions in the description, and provided examples of reference texts that provide hybridization conditions. However, one skilled in the art hardly needs to have the conditions provided, given that he or she is so familiar with a basic technique of molecular biology.

Therefore, since the specification is written for those skilled in the art, who are very familiar with the concept and practice of nucleic acid hybridization, Applicant asserts that the claims are not indefinite.

Based on these arguments and claim amendments, Applicant respectfully requests reconsideration and withdrawal of the rejections made under 35 U.S.C. 112, second paragraph.

Rejections Under 35 U.S.C. 103

The Examiner rejected claims 1, 2, 6-8 and 10 under 35 U.S.C. 103, as obvious over the combination of Kumar et al. (Biochem Biophys Res Commun. 235(3): 474-478, 1997) and Baumgarten et al. (Trends Cardiovasc Med. 10(5): 216-223, 2000). Applicant respectfully traverses the rejection and requests reconsideration. Claim 2 has been canceled, rendering the rejection of that claim moot.

According to the Examiner, Kumar teaches that expression of Fit-1/ST2 is induced by proinflammatory stimuli, including TNF and IL-1. The experiments shown in Kumar that exhibit that stimulation by TNF and (to a much lesser extent) IL-1 leads to increased expression of Fit-1/ST2 mRNA are *in vitro* experiments that use purified cytokines to stimulate quiescent fibroblasts. These are not experiments that are intended to mimic *in vivo* conditions such that conclusions can be drawn about stimulation of Fit-1/ST2 cells other than fibroblasts, or about stimulation of Fit-1/ST2 under physiological conditions.

According to the Examiner, Baumgarten teaches that cardiovascular disease is associated with elevated levels of cytokines, such as TNF and IL-1. From this, the Examiner concludes that it would have been obvious for one of ordinary skill in the art to use cytokine-inducible genes or encoded polypeptides in diagnosis of cardiovascular disease. Applicant notes that Table 2 shows that there is variability in the expression of cytokines in heart failure: while TNF appears to be upregulated in the majority of the studies tabulated, IL-1 appears to be upregulated in only 1 of the 5 studies that measured IL-1. Furthermore, Baumgarten does not report that the studies examined whether genes were upregulated by the expression of TNF. In fact, the most that Baumgarten states about TNF levels in the context of diagnosis (page 216, right column) is that "TNF levels may be predictive of NYHA [New York Heart Association] class and clinical outcome." That statement is hardly a definitive conclusion of the diagnostic utility of this one cytokine. In addition, Baumgarten states that "there is little clinical evidence that supports an important role for IL-1, IL-2 of IFN-γ in heart failure." Page 217, right column.

The combination of references cited is insufficient to support a *prima facie* case of obviousness, for the following reasons. First, there is no link in these references between cardiovascular conditions and Fit-1/ST2 expression. Baumgarten reports that TNF appears to be upregulated in heart failure, but that IL-1 is not. Kumar reports that, under certain artificial conditions having nothing to do with heart failure or other cardiovascular conditions, purified TNF induces Fit-1/ST2. It is a critical omission, however, that neither Baumgarten nor Kumar teach or suggest that Fit-1/ST2 is upregulated following heart failure.

Second, there is nothing in these two references that would provide one of ordinary skill in the art with the requisite reasonable expectation of success. The Examiner stated that it would have been obvious for the skilled artisan to incorporate the teachings of Baumgarten and Kumar to examine "common cytokine-inducible genes, or their encoded polypeptides, in methods of diagnosing cardiovascular disease." Office Action at page 10. Applicant respectfully disagrees.

In the context of the many genes that are upregulated by TNF (see, e.g., Tang et al., J Mol Cell Cardiol. (2004) 36(4):515-530, which indicates that the expression of >1000 genes are altered in the heart upon cardiac-specific over-expression of TNF), one of ordinary skill in the art would not be motivated to examine Fit-1/ST2 expression as indicative of cardiovascular conditions based on the teachings of these two references. No correlation shown in the combination of Kumar and Baumgarten between Fit-1/ST2 expression and cardiovascular disorders. Further more, cytokines such as TNF induce many of genes; the combination of references does not disclose that Fit-1/ST2 should be selected from among the many TNF-induced genes as diagnostic for cardiovascular conditions – that is Applicant's contribution.

The teachings of the two cited references do not provide sufficient guidance such that the skilled person would find it obvious to look at ST2 in particular. Given the large number of TNF-upregulated genes known in the art at the time of filing, and the lack of specific teaching of ST2 induction under physiological conditions (let alone in cardiovascular conditions), it appears that the Examiner has used a hindsight reconstruction of the claimed invention as a guide to selecting and interpreting the cited references.

In addition, Applicant has discovered that a different mechanism, mechanical strain or overload, leads to increased Fit-1/ST2 expression. This is not described or suggested in any way by either of the cited references or the combination thereof.

Because the combination of the cited documents does not teach or suggest diagnosis of cardiovascular conditions based on increases in Fit-1/ST2 expression, there is no reason whatsoever why one of ordinary skill in the art would be motivated to select this gene for diagnosis of cardiovascular conditions. The only way to arrive at such a conclusion is through

the application of hindsight reconstruction of Applicant's invention based on the teachings in Applicant's specification. The combination of the Kumar and Baumgarten references simply does not provide adequate teaching or adequate motivation to modify the teaching that is presented in a manner that would result in Applicant's invention, absent application of hindsight. This is improper.

Applicant notes that "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." In re Wesslau, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965); see also In re Mercer, 515 F.2d 1161, 1165-66, 185 USPQ 774, 778 (CCPA 1975); In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive.... Appellant argues... hindsight reconstruction or at best,... 'obvious to try'.... We agree with appellant.").

Therefore, Applicant asserts that the Examiner has failed to meet the burden of providing the evidence necessary to establish a prima facie case of obviousness. Applicant respectfully requests reconsideration of the rejection of the claims as unpatentable for obviousness.

Double Patenting

The Examiner provisionally rejected claims 1, 6-8 and 10 under the judicially-created doctrine of obviousness-type double patenting over claims 1-3, 7 and 9 of copending application serial number 10/435,482. Applicant respectfully traverses the rejection.

As noted by the Examiner in making this a provisional rejection, the claims of the cited application have not yet been allowed. Therefore, Applicant believes that it is premature to address the rejection, and respectfully requests reconsideration.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

LEE, Applicant

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